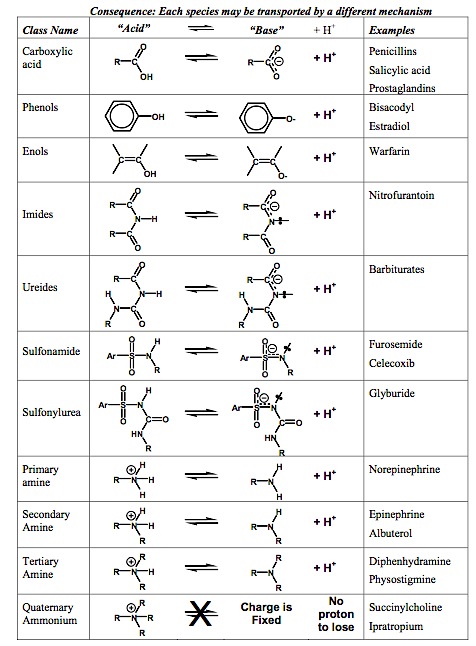
**DRUG TRANSPORT OBJECTIVES**

1. **Recognize that barrier exist to the movement of a drug around the body** 
   1. Barriers to drug absorption and distribution
      1. Cell membranes composed of amphipathic molecules to absorbed into body and enter cells in tissues
      2. Most drugs are not natural metabolites so most carrier for them do not exist
         1. Therefore, most drugs must be **soluble in lipids and fats** to cross the membrane which is a barrier to polar hydrophilic molecules
      3. To access cell membrane lipid bilayer which is bathed in aqueous media, most drugs **must also be** **soluble in water**
      4. Ideally drug should have solubility in both fat and water—it should have a favorable partition coefficient
         1. Partition coefficient –a substance added to a mix of oil and water will dissolve in each. At equilibrium the chemical potential (free energy) will be the same in both phases
            1. Measure concentration of drug in oil and water phases
            2. PC= [drug**]** in oil/ [drug**]** in water
         2. ^^most important property of a drug
2. **Describe how a drug’s lipid/water partition coefficient relates to its transport across biological membranes** 
   1. Ideally drug should have solubility in both fat and water—it should have a favorable partition coefficient
      1. Partition coefficient –a substance added to a mix of oil and water will dissolve in each. At equilibrium the chemical potential (free energy) will be the same in both phases
         1. Measure concentration of drug in oil and water phases
         2. PC= [drug**]** in oil/ [drug**]** in water
3. **From its structure identify a drug as neutral, a weak acid, a weak base or the salt of a strong acid or base** 
   1. Classification
      1. Neutral uncharged drugs
         1. Not an acid or base so their Partition coefficient (PC), solubility and other properties are independent of pH
         2. PC is strongly dependent on relative number of hydrophobic (nonpolar) carbon groups and hydrophilic (polar) groups like -OH
         3. Ex: Ethanol, Sorbitol, Estradiol, Dexamethasone
      2. Weak acids and weak bases and their salts
         1. Acid (HA) can donate a proton to a base
            1. Weak acid is a compound/drug that can donate a proton reversibly to water
         2. Base (B) can accept a proton from an acid
            1. Weak base is a compound/drug that can accept a proton reversibly from water
         3. The term “weak” indicates that both the ionized and un-ionized forms of the drug are present in equilibrium in the aqueous solution
         4. The relationship between the concentrations of the two drug species is defined by the dissociation constant or equilibrium constant (Ka) for the acid form: **Ka = [Base]\*[H+]/[Acid]** 
            1. This tells us that the concentration ratio of Base: Acid is a function of the pH as well as the pKa. To use this eqn, you must be able to identify which drug species is the acid and which is the base
         5. Salicylic acid: Typical weak acid drug
            1. Lipid soluble acid and a water soluble base
         6. Diphenhydramine: Typical weak base drug
            1. Lipid-soluble Base & Water-soluble Acid
      3. Salts of strong acids and strong bases
         1. Strong acids and bases, and more importantly, salts of a strong acids or bases are always, i.e. completely, dissociated in aqueous solution and do not lose nor bind protons in aqueous solution
            1. The drug molecules are always charged  EXAMPLES
            2. Anions of strong acids, R-OSO3-, R-OPO3-
            3. Cations of strong bases, R4-N+ quaternary ammonium group
         2. Note also that for drugs with multiple weak acidic or basic groups, the concentration of uncharged species is negligible and they will behave like strong acids/bases
         3. **IPRATROPIUM**: a quaternary ammonium drug
            1. For atropine at pH7, [Base]:[Acid] = 1:500

Ipratropium always carries a + charge, it has no H+ that can be  removed

* + - 1. **HEPARIN:** strongly acidic drug
         1. Heparin is a large molecule with a large number of strongly acidic sulfonate groups and many hydroxyl groups. There are probably few drugs with a lower partition coefficient
         2. Many charged groups and very low pKa of sulfuric acid make it impossible to form an uncharged structure
         3. Even without a charge, sugar molecules have very low partition coefficients
      2. **AMINOGLYCOSIDES**: drugs with multiple positive charges
         1. Aminoglycosides such as tobramycin have multiple weak basic groups
         2. Multiple charges make it essentially impossible to form an uncharged structure
         3. Even without a charge, sugar molecules have very low partition coefficient

1. **Explain why many drugs are weak acids or weak bases** 
   1. This is necessary because drugs need to be able to pass through cell membranes (that excludes strong acids and bases) and dissolve in the stomach and blood (that's favor acids and bases but excludes neutral uncharged drugs). If a compound is too basic or acidic, it won't be able to cross the cell membranes and leave the digestive tract; if it's not acidic or basic at all, it won't dissolve well in the blood so it won't be carried efficiently throughout the body.
   2. acids and bases gain and lose protons, which gives them ionic charges. Charged particles dissolve well in water, so acids and bases dissolve well. Charged particles can't pass through layers of uncharged molecules like those that make up the cell membrane, though.
   3. \*\*Weak acids and bases have the advantage that they're sometimes in their ionized state and sometimes in their unionized state, so they can dissolve, get through the cell membrane and then re-dissolve in the blood.
2. **Describe how to calculate the percentage of a weakly acid or basic drug that exists in charged and uncharged forms at a given pH using the Henderson-Hasselbalch equation** 
   1. Henderson-hasselbalch equation
      1. Permits one to calculate the ratio of base/acid for any pH if the Ka or pKa are known
         1. Ka = [Base]\*[H+]/[Acid] 🡨take log
         2. logKa = log([Base]/ [Acid]) + log[H+]= -pKa= log([Base]/ [Acid]) – pH (rearrange)
         3. **pH-pKa = log([Base]/ [Acid])🡨H-H equation**
         4. [Base]/ [Acid]= 10 ^(pH – pKa)
   2. EXAMPLES
      * 1. Salicylic acid: Typical weak acid drug
           1. Lipid soluble acid and a water soluble base
           2. For salicylic acid

Ka = [Base].[H3O+]/[Acid] = 10-3

*or* Ka = {[Base]/[Acid]}\*[H3O+]

Consequently, for salicylate at pH 7 (i.e. [H3O+] = 10-7)

Ka = 10-3 = {[Base]/[Acid]} x 10-7

And therefore the ratio [Base]:[Acid] = 10000:1

Thus, only one part in 10,000 is in the uncharged acid form (salicylic acid), while 99.99% is in the charged anionic form (i.e. salicylate). This is only true in water. The partition coefficient of the charged species is likely to be very poor (low) while that of the uncharged acid will be high. Thus, in oil or a lipid membrane, the concentration of the neutral form might be much higher than that of the charged species.

* + - 1. Diphenhydramine: Typical weak base drug
         1. Lipid-soluble Base & Water-soluble Acid
         2. For diphenhydramine

Ka = [Base].[H3O+]/[Acid] = 10-9

*or* Ka = {[Base]/[Acid]}.[H3O+]

Consequently, for diphenhydramine at pH 7 (i.e. [H3O+] = 10-7)

Ka = 10-9 = {[Base]/[Acid]} x 10-7

And therefore, the ratio [Base]:[Acid] = 1:100

Thus, only one part in 100 is in the uncharged basic form (i.e. tertiary amine), while 99% is in the charged cationic form (i.e. tertiary ammonium). This is only true in water. The partition coefficient of the charged species is likely to be very poor (low) while that of the uncharged base will be high. Thus, in oil or a lipid membrane the concentration of the neutral form is likely to be much higher than that of the charged species.

1. **Explain the importance of passive diffusion in efficient absorption from the GI tract, and distribution to certain organs, e.g. the CNS** 
   1. Passive Diffusion like any passive transport simply uses the concentration gradient of the transported species acors the membrane and to drive transport (it is a spontaneous downhill process that dissipates the gradient)
   2. Important because drugs and nutrients must diffuse across lipid bilayer membranes to get absorbed into the blood
      1. So they must have favorable PC
      2. Have an uncharged form
         1. Neutral drugs
         2. Weak acids and bases
2. **Describe the mechanism of transport of neutral drugs across lipid bilayers** 
   1. **Passive Diffusion** like any passive transport simply uses the concentration gradient of the transported species acors the membrane and to drive transport (it is a spontaneous downhill process that dissipates the gradient)
   2. Rate of transport will be proportional to the difference in concentration across the membrane
      1. Rate= k(C1-C2)
         1. At equilibrium the concentration of drug in the membrane (Cm)/C1= PC
      2. K depends on PC—the higher the concentration in the membrane the faster it will be transported
   3. So in the case of neutral drugs, who have favorable partition coefficients will cross lipid membranes
3. **Describe the mechanism of transport of weak acids and bases across lipid bilayers** 
   1. Weak base
      1. These exist as either water soluble and lipid insolulble charged form (conjugate acid) OR as potentially lipid soluble, uncharged form (base)
      2. Only the neutral uncharged form crosses the membrane; however, if the pH is the same and remains the same on both sides of the membrane, transport of the drug will take place until the concentration is the same on each side
      3. The rate of transport will depend on the **concentration** of the **uncharged form** (i.e. total **amount of drug** present and its **pKa and the pH**) and the **partition coefficient** of the uncharged form
   2. Weak Acid
      1. These exist as either water soluble and lipid insolulble charged form (conjugate base) OR as potentially lipid soluble, uncharged form (acid)
      2. Only the neutral uncharged form crosses the membrane; however, if the pH is the same and remains the same on both sides of the membrane, transport of the drug will take place until the concentration is the same on each side of the membrane
      3. The rate of transport will depend on the **concentration** of the uncharged form (i.e. total **amount of drug** present and its **pKa and the pH**) and the **partition coefficient** of the uncharged form
4. **Explain the effect of pH on the rate of transport of weak acids and bases across lipid bilayers.** 
   1. Weak Base
      1. The pH ***does not*** affect the equilibrium distribution of the transported form, **i.e. the uncharged base**
      2. The pH ***does not*** change the Ka (pKa)
      3. Remember, however, the pH determines the ratio of base:acid
      4. Consequently, the concentration of charged form of the basic drug will increase in proportion with the increase in proton (H+) concentration
      5. \*\*weak basic drugs will accumulate in compartments in which the pH is more acidic than the blood
   2. Weak acid
      1. The pH does not affect the equilibrium distribution of the transported form (the uncharged acid)
      2. The pH ***does not*** change the Ka (pKa)
      3. Remember, however, the pH determines the ratio of base:acid
      4. Consequently, the concentration of charged form of the acidic drug will change inversely with the proton (H+) concentration
      5. \*\*weak acidic drugs will accumulate in compartments in which the pH is more alkaline than the blood
5. **Describe the effect of pH gradients on the equilibrium distribution of weak acids and weak bases and the concept of “ion trapping”** 
   1. The difference in concentrations of weak acids and bases between blood and different compartments brought about by a difference in pH is frequently referred to as “ion trapping”
      1. \*important in renal elimination of drugs
   2. **Examples pH**
      1. **Stomach 2**
      2. **Vaginal Secretions 3.4-4.2**
      3. **Prostatic Secretions 6.4**
      4. **Urine 5-8**
      5. **Breast Milk 6.4**
      6. **Jejunum, Illeum 7.5-8.0**
6. **Explain the role of capillary pores in the distribution of drugs to most tissues and identify their most common locations and describe the nature of the blood brain barrier** 
   1. ***PORES*** 
      1. Pores are non-selective holes for the passage of free molecules from the capillaries to the interstitium
      2. Only the size of the molecule or protein binding restricts transport
         1. Heparin is essentially limited to plasma compartment
      3. For most drugs pH, pK and lipid solubility/partition coefficient (PC) have no effect  on the transport
      4. This is a very effective and hence the **most important mechanism** for the entry of most drugs into most tissues
      5. **CONSEQUENCE*: the rate of entry of the drug into most tissues is not limited by lipid solubility, but by the blood flow***
   2. ***LOCATION OF PORES***
      1. Pores are found in most capillaries 
         1. The blood-brain barrier – pores are absent in brain capillaries
      2. Kidney glomerular capillaries contain large pores
      3. Liver sinusoids and spleen lack a real endothelium, e.g. hepatocytes are in direct  contact with blood
7. **Identify the major locations where drugs undergo active transport, the ability to drive transport “uphill” and the potential for drug interactions** 
   1. *Active transport* couples the transport of a drug to a chemical reaction or the transport of another species using energy from the cell to drive transport, i.e. it is not spontaneous, and for a given species can be uphill to *generate* a gradient
   2. Transport proteins are required to couple the input of energy to the movement of the drug or couple the flux of one molecule to that of another
      1. Unlike diffusion through the bilayer, transport only occurs in cells which express these proteins and hence occurs in specialized locations
   3. *Where does active transport take place?* 
      1. Proximal tubule of kidney nephron
      2. Hepatocytes, GI tract
      3. Brain (BBB), choroid plexus (blood/CSF), etc.
   4. Role of active transport can be viewed as to protect the body against xenobiotics
      1. Transporters in liver, kidney and intestine epithelia have important effects on  *absorption* and *elimination*
      2. Transporters in tissues such as brain, testis, placenta also help prevent entry of harmful xenobiotics, but also can limit *distribution* of therapeutic drugs to those tissues
   5. Two major families of transporters are found in the body which are able to transport many drugs and other xenobiotics and their metabolites
      1. ABC (“ATP binding cassette”) transporters
      2. SLC (solute carrier) superfamily transporters
   6. Because of broad selectivity, drugs with same charge can compete with each other, which can produce drug interactions
8. **Identify the two major families of drug transporters, the ABC and SLC families.** 
   1. *SLC SOLUTE CARRIER SUPERFAMILY*
      1. Includes 315 transporters in 48 families including
         1. OAT, OATP, OCT, MATE families of transporters
      2. Catalyze facilitated transport (uniport), and secondary ion coupled transport, (antiport and symport)
      3. Important for drugs with net charges, including
         1. Charged forms of weak bases or acids
         2. Permanently charged drugs
      4. 1) ORGANIC CATION TRANSPORTERS, OCT1, OCT2 AND OCT3
   2.   Transport hydrophobic and hydrophilic cations
   3.   Catalyze facilitated transport or “uniport” with *net charge* movement
   4. *ABC (“ATP BINDING CASSETTE”) TRANSPORTERS*
      1. Includes 49 different transporters in 7 families, important examples:
         1. P-glycoprotein (MDR1), (MRP2), BCRP
      2. ATP hydrolysis provides energy to drive transport directly
      3. **Function is to pump drugs out of cells**
      4. ***WHERE DOES ACTIVE TRANSPORT TAKE PLACE?***
         1. Proximal tubule of kidney nephron
            1. Important for excretion of some drugs
         2. Hepatocytes, GI tract
            1. Transporters in liver and intestine epithelia are most important for  pharmacokinetics of ***absorption*** and ***elimination***
            2. Important for transport of drugs into cells for biotransformation
            3. Important for transport of drugs out of cells into bile or blood
         3. Vascular endothelium in brain, choroid plexus (barrier between blood and CSF), and other locations
            1. Protects tissue by pumping drugs out of tissue into the blood
9. **Describe selectivity of the OCT and OAT families and their role in drug influx** 
   1. SLC
      1. **ORGANIC CATION TRANSPORTERS, OCT1, OCT2 AND OCT3** 
         1. Transport hydrophobic and hydrophilic cations
         2. Catalyze facilitated transport or “uniport” with *net charge* movement
         3. Consequently, since membrane potential is negative inside cells, the ***electrochemical*** gradient for cationic drugs is inward and **OCTs mediate influx** of the drug across the cell membrane
            1. Energy comes from the NaK ATPase, which maintains the membrane potential
      2. **MATE (MULTIDRUG AND TOXIN EXTRUSION) AND OCTN FAMILIES**
         * 1. Catalyze electroneutral drug/H+ antiport
           2. Transport gradient depends on pH gradient not the membrane potential hence  these transporters provide efflux pathway for cationic drugs

A separate Na+/H+ antiporter generates/maintains the H+ gradient

Energy comes from the NaK ATPase, which maintains the Na+ gradient

* + 1. **3) ORGANIC ANION TRANSPORTERS, OAT1, OAT2, OAT3, OATP** 
       1. Mediate **influx** of hydrophilic and hydrophobic anions (also some cations and  neutral substances)
          1. OAT1 and OAT3, transport many low MW anions, drugs, PGE2, urate
          2. OAT2 transports nucleotides, e.g. cGMP
       2. *Electrochemical gradient* for anions does not normally favor net *influx of negative charge*. Influx is made energetically favorable, by coupling the ***influx*** of the anionic drug with one negative charge OA- to the ***efflux*** of - ketoglutarate2- with 2 negative charges, so there is net efflux of negative charge (OAT1, OAT3)
          1. -ketoglutarate is replenished by entry with Na+ via NaDC3
          2. Energy comes from the NaK ATPase, which maintains the Na+ gradient

OATP, e.g. OATP1B1 is important in liver

1. **Describe selectivity of P-glycoprotein and its role in ATP driven drug efflux** 
   1. **P-GLYCOPROTEIN (P-gp; MDR1)** 
      1. Transports mostly, ***large neutral*** or positively charged ***hydrophobic*** drugs
      2. These drugs/xenobiotics often have good partition coefficients and can enter  cells by passive diffusion
      3. P-glycoprotein provides a mechanism for the cell to expel them from the cytoplasm to minimize potential harm
   2. OTHER ABC TRANSPORTERS
      1. **MULTIDRUG RESISTANCE PROTEIN 2 (MRP2)** 
         1. Transports mostly, amphiphilic organic anions, especially glucuronide, glutathione and SO4 conjugates
      2. **BREAST CANCER RESISTANCE PROTEIN (BRCP)**
         1. Neutral and negatively charged drugs, e.g. SO4 conjugates